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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
09/544,910	04/07/00	HUANG	Y	06510/121US1

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1642	12

DATE MAILED: 08/09/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/544,910	HUANG ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 May 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above claim(s) *12-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-35* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The Amendment under 37 CRF § 1.111, which is responsive to the previous Office Action mailed on January 29, 2001 (Paper No. 9), filed on May 7, 2001 in Paper No. 10 is acknowledged and has been entered. Claims 1 and 5 are amended.

2. The Declaration of Yadong Huang under 37 CFR § 1.132 has been timely filed in Paper No. 11 and has been entered. The merit of the Declaration has received full consideration.

3. Claims 1-35 are pending in the application. Claims 12-35 have been withdrawn from further consideration pursuant to 37 CFR § 1.142(b) as being drawn to a non-elected invention. Claims 1-11 are currently under prosecution.

4. The text of those sections of Title 35, US Code not included in this Office Action can be found in the prior Office Action.

Specification

5. The disclosure is objected to because of the following informalities: The upper margins are not large enough to accommodate the holes that are necessarily punched in order to attach the papers to the file wrapper without removing a portion of the text. A substitute specification with larger margins to accommodate the holes is required.

Priority

6. In response to the requirement set forth in the previous Office Action (Paper No. 9) the first line of the specification is amended by Paper No. 10 to contain a specific reference to the prior application to which the instant application claims benefit of the earlier filing date. Applicant has now complied with the conditions for receiving the benefit of an earlier filing date under 35 USC § 119(e).

Summary of the Claim Rejections Made in the Prior Office Action

Claim Rejections – 35 USC § 112, first paragraph

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. In the previous Office Action (Paper No. 9), claims 1-11 were rejected under 35 USC § 112, first paragraph because the disclosure is not considered to meet the written description requirements of 35 USC § 112, first paragraph for the reasons set forth therein. Essentially, the reason given is that the subject matter of the claimed invention was not described in the specification in such a way as to reasonably convey to the skilled artisan that Applicant had possession of the invention at the time the application was filed. In particular, the Examiner cited the lack of disclosure identifying a specific agent that can be used to practice the invention successfully, the lack of exemplification, prophetic or otherwise demonstrating that the invention can be used successfully to reduce the plasma level of VLDL and triglycerides in a host, and the lack of exemplification, prophetic or otherwise demonstrating that the invention can be used efficaciously to treat a host suffering from a disease condition associated with elevated levels of VLDL and/or triglycerides as supportive evidence of the conclusion that Applicant was not in possession of the claimed invention at the time of filing.

9. In the previous Office Action (Paper No. 9), claims 1-11 were rejected under 35 USC § 112, first paragraph because the teachings of the specification cannot be extrapolated to the enablement of the invention commensurate in scope with the claims for the reasons set forth therein. Essentially, the reason given is that in the absence of sufficient guidance and exemplification commensurate in scope with the claims, extensive and undue experimentation would necessarily have to be performed first in order to practice the invention with a reasonable expectation of success. Furthermore, in the absence of working exemplification and in view of the high level of unpredictability

in the art, the skilled artisan would not accept the assertion that any agent, the chemical nature of which is undisclosed, which at least reduces the amount of plasma active apoE can be used to effectively treat a host suffering from a disease condition associated with elevated plasma levels of VLDL and/or triglycerides. Nevertheless, it is reasonably clear that since the specific identity of a suitable agent that can be used to practice the invention successfully remains a mystery, the skilled artisan would be required to perform extensive and undue experimentation, first, to identify a candidate agent and second, to determine whether the candidate agent can be used safely and effectively. The claims encompass a multitude of non-working embodiments and finding a working embodiment among the possibilities, assuming that one can be found would require undue experimentation. Therefore, the recitation of a catalog of putatively effective generic agents is insufficient to enable the skilled artisan to practice the invention with a reasonable expectation of success without undue experimentation.

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. In the previous Office Action (Paper No. 9), claims 1-11 were rejected under 35 USC § 112, second paragraph because claims 1 and 5 are indefinite. Claims 1 and 5 are indefinite because the claims do not recite a positive process step that clearly relates back to the preamble of the claims.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. In the previous Office Action (Paper No. 9), claims 1-11 were rejected under 35 U.S.C. 102(b) as being anticipated by Ditschuneit, et al, as evidenced by Pedreno, et al

and Durrington, et al for the reason set forth therein. In summary of those reasons, Ditschuneit, et al teaches a method for treating patients diagnosed with a disease associated with elevated plasma levels of VLDL and triglycerides. Specifically, Ditshuneit, et al administer to the patients an effective amount of gemfibrozil to reduce the concentrations of both VLDL and triglycerides in the patient's serum. As evidenced, by the teachings of Pedreno, et al, gemfibrozil causes a reduction in the level of plasma active apoE. Therefore, the method of Ditschuneit, et al causes a reduction in plasma active apoE. Thus, all the limitations of the claims are anticipated by the teachings of Ditschuneit, et al.

14. In the previous Office Action (Paper No. 9), claims 1, 3-8, 10, and 11 were also rejected under 35 U.S.C. 102(b) as being anticipated by Yoshino, et al for the reason set forth therein. In summary of those reasons, Yoshino, et al teach a method for treating patients diagnosed with a disease associated with elevated plasma levels of VLDL and triglycerides. Specifically, Yoshino, et al administer to the patients an effective amount of pravastatin to reduce the concentrations of apoE, VLDL, and triglycerides in the patient's plasma. Thus, all the limitations of the claims are anticipated by the teachings of Ditschuneit, et al.

15. In the previous Office Action (Paper No. 9), claims 1, 3-8, 10, and 11 were also rejected under 35 U.S.C. 102(b) as being anticipated by Connor, et al for the reason set forth therein. In summary of those reasons, Connor, et al teach a method for treating patients diagnosed with a disease associated with elevated plasma levels of VLDL and triglycerides. Specifically, Connor, et al administer to the patients an effective amount of dietary n-3 fatty acids to reduce the concentrations of apoE, VLDL, and triglycerides in the patient's plasma. Thus, all the limitations of the claims are anticipated by the teachings of Connor, et al.

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. Claims 1, 2, 4-9, and 11 were rejected under 35 U.S.C. 103(a) as being unpatentable over Huff, et al in view of Huang, et al for the reason set forth therein. In summary of those reasons, Huff, et al teach an antibody known to block binding of apoE to the LDL receptor and Huang, et al teach that the accumulation of apoE in a mouse causes the occurrence of elevated levels of VLDL and triglycerides in the mouse. The Examiner stated that it would have been obvious to one of ordinary skill to combine the teachings of Huff, et al and Huang, et al to administer to a patient an effective amount of the antibody of Huff, et al to reduce the levels of VLDL and triglycerides in said patient by reducing the level of active apoE in said patient's serum. Essentially, the examiner stated that one of ordinary skill in the art would have been motivated to combine the teachings of Huff, et al and Huang, et al in order to satisfy a long-felt need for an effective treatment that would reduce the occurrence of atherosclerosis in patients.

Response to the Declaration under 37 USC § 1.132

18. The Declaration under 37 CFR § 1.132 filed on May 7, 2001 in Paper No. 11 is sufficient to overcome the rejection of claims 1, 2, 4-9, and 11 based upon a specific reference applied under 35 USC § 103(a), namely Huang, et al.

Response to the Amendment under 37 CFR 1.111

Claim Rejections – 35 USC § 112, first paragraph (written description)

19. The Amendment filed under 37 CFR § 1.111 filed on May 7, 2001 in Paper No. 10 has received the Examiner's full and careful consideration, but the amendment to claims 1 and 5 is insufficient to overcome the rejection and Applicants' arguments are

not found persuasive. The reason that the amendment to claims 1 and 5 is insufficient to overcome the rejection and that the arguments are not found persuasive is set forth below:

In the rebuttal, Applicants contend claims 1 and 5 have been amended to more particularly point out and distinctly claim the invention (page 3, paragraph 3). Applicants state the basis for the invention is a novel discovery, which constitutes the observation that over-expression and accumulation of apoE causes hypertriglyceridemia by stimulating the production of VLDL and impairing the lypolysis of VLDL (page 4, paragraph 2). With respect to the 35 USC § 112, first paragraph rejection made in section 6 of the prior Office Action, Applicants submit that one skilled in the art *would* recognize that they had possession of the invention at the time the application was filed because the specification discloses "a detailed list of many agents suitable for use in the present invention" (page 4, paragraph 3). Furthermore, Applicants assert that had the observation, which is the basis for the invention not been made, "the artisan would *not* have known to look within these broad classes for agents which could reduce apoE and would not have known to use these agents to reduce VLDL production by reducing active apoE" (page 5, paragraph 2). Additionally, Applicants state that "the specification does describe specific **antibodies of interest** on page 14, lines 6-11" (emphasis added) (page 4, paragraph 4), disagreeing with the Examiner's assertion that one skilled in the art cannot predict whether or not an agent that can be used to practice the invention successfully actually exists or can be created, because "agents which directly effect apoE are already known in the art" (page 5, paragraph 3). Applicants argue that "it is well-established that a 'patent need not teach, and preferably omits, what is well known in the art'" (paragraph bridging pages 4 and 5), suggesting that the disclosure of specific antibodies that bind apoE is sufficient to reasonably convince one skilled in the art that they had possession of the invention at the time the application was filed.

The arguments are not found persuasive because regardless of the fact that Applicants' disagree with the Examiner, neither the disclosure nor the Amendment provides factual evidence that would reasonably convince the skilled artisan that Applicant was in possession of the *claimed* invention at the time the application was

filed. As amended, the claims are drawn to a method for reducing the plasma level of VLDL in the plasma of an animal, and in particular a patient suffering from a disease associated with elevated levels of VLDL. However, as set forth in the prior Office Action, the specification is devoid of prophetic and working exemplification. Moreover, it was noted that the specification fails to specifically identify even one agent that can be used to practice the claimed invention successfully. Applicant rebuts that the specification discloses some references that teach specific antibodies that bind apoE; however, there is no factual evidence that any one of the "antibodies of interest" can be used effectively to reduce the level of apoE or VLDL in the serum of an animal or patient. Clearly, the referenced antibodies are of interest because Applicant has conceived an idea that a neutralizing antibody that binds apoE might be capable of blocking the activity of apoE. However, there is no factual evidence that the antibodies of interest are capable of neutralizing the activity of apoE or for that matter, capable of reducing the level of apoE in the serum of animals or patients, as the claims require. Applicant is reminded that evidence of Applicants' conception of the invention does not constitute evidence of Applicants' possession of the invention. In other words, the basis for the invention is not at issue in the examination; at issue, however, is the lack of factual evidence that the Applicant can use the invention to reduce the level of VLDL in an animal or patient suffering from a disease such as hyperlipidemia. The disclosure of a list of generic agents that can be screened by the artisan in order to identify one species that is possibly capable of fulfilling the requirements of the claims, which includes nearly all naturally occurring and synthetic molecules, is not viewed as sufficient evidence that Applicant invented a treatment method as claimed. Therefore, the disclosure is merely viewed as an invitation to the skilled artisan to experiment in an effort to discover an agent that might possibly be used to practice the invention. Applicant essentially claims the use of an invention that has yet to be made.

In summary, while the merit of the Amendment has received full consideration, Applicants' arguments are not persuasive, because the preponderance of evidence suggests that Applicant did not have possession of the invention at the time the application was filed. Therefore, the disclosure fails to meet the written description

requirement of 35 USC § 112, first paragraph. For the reason set forth above, the rejection made in the previous Office Action in section 6 under 35 USC § 112, first paragraph is maintained.

Claim Rejections – 35 USC § 112, first paragraph (enablement)

20. The Amendment filed under 37 CFR § 1.111 filed on May 7, 2001 in Paper No. 10 has received the Examiner's full and careful consideration, but the amendment to claims 1 and 5 is insufficient to overcome the rejection and Applicants' arguments are not found persuasive. The reason that the amendment to claims 1 and 5 is insufficient to overcome the rejection and that the arguments are not found persuasive is set forth below:

Applicants contend claims 1 and 5 have been amended to more particularly point out and distinctly claim the invention (page 3, paragraph 3). In their rebuttal Applicants state that "practitioners in the chemical and molecular biology arts frequently engage in extensive modification of reaction conditions and complex and lengthy experimentation where many factors must be varied to succeed in performing an experiment or in producing a desired result" (page 6, paragraph 3). Furthermore, Applicants state that "the Federal Circuit has found that such extensive experimentation is not undue" (page 6, paragraph 3). Accordingly, Applicants argue that "a considerable amount of experimentation is permissible" (page 7, paragraph 1) and therefore the skilled artisan would not be subject to undue experimentation in learning to practice the invention with a reasonable expectation of success. Applicants state that "one of skill in the art of using agents to obtain a desired result in a host routinely performs screening of agents to identify those that are effective in achieving the desired result and to determine the appropriate dosage and route of administration" (page 7, paragraph 2). Applicants contend that this is evidenced by the teachings of Gura, et al. Applicants argue therefore that the provision of a list of generic agents (e.g., antibodies) is sufficient to enable one skilled in the art to proceed with extensive experimentation in an effort to determine whether there actually is an agent that can be used to practice the claimed invention successfully. Furthermore, Applicants state that the disclosure of methods for

screening and identifying a suitable agent from among the genus of agents to which the claims are drawn is "all that is needed" (page 7, paragraph 4).

It is fairly clear that Applicants believe an agent will be discovered one day that can fulfill the requirements of the claims. Of course, the artisan may have to screen hundreds of antibodies, hundreds of small organic molecules, hundreds of antisense RNA molecules, and hundreds and hundreds of every other type of molecule imaginable in order to identify one such molecule that can be used to reduce the level of apoE and VLDL in the serum of an animal, because it is clear that Applicants have not yet identified a specific agent that fulfills the requirements of the claims. Nevertheless, Applicants believe that the amount of experimentation that would be required to do so would be routine and therefore not undue or excessive in nature. However, the Examiner notes that Applicants' discourse on the amount of experimentation that the court considers reasonable tends to suggest that Applicant truly did not have possession of the invention at the time the application was filed. Otherwise, if Applicant were in possession of the invention, why would it be necessary to argue that the extensive experimentation necessary to identify a suitable agent is not excessive? To the contrary, if Applicant actually had possession of the invention, it would not be necessary to screen thousands of candidate agents, but only necessary to determine the effective and tolerable dose and the most efficacious route and schedule of administration. Certainly, the extent of experimentation needed to determine the effective and tolerable dose and the most efficacious route and schedule of administration of the identified agent would not constitute undue experimentation, as the court has indicated. However, contrary to the opinion of Applicants, the Examiner contends that the amount of experimentation that would be required to practice the invention with a reasonable expectation of success is unwarranted, because the specification does not teach which, if any of the many thousands of putative agents that are encompassed by the claims can be used effectively to reduce the level of apoE and VLDL in an animal or a patient. Certainly, in the absence of exemplification commensurate in scope with the claims and in view of the unpredictability in the art of drug discovery, as evidenced by the teachings of Gura, et al (cited in the previous Office

Action), one skilled in the art cannot practice the claimed invention with a reasonable expectation of success without extensive, undue experimentation.

Additionally, Applicant is reminded that the claims are not limited to an antibody or even to an antibody that specifically binds apoE, but rather to a genus of undisclosed and probably uncharacterized agents. Nonetheless, there is no disclosure of factual evidence in the specification or in the Amendment that indicates that an antibody, even an antibody that specifically binds apoE can be used effectively to reduce the level of apoE. With regard to the limitation in claims 3 and 10, there is no factual evidence of record that a neutralizing antibody, or especially one of the "antibodies of interest" that specifically bind apoE can effectively reduce the level of expression of apoE. In fact, one skilled in the art would not expect an antibody that binds apoE to be capable of reducing the level of expression of apoE; actually, if the expression of apoE is regulated by a feed-back mechanism (i.e., the expression of apoE is triggered upon depletion of apoE), then one skilled in the art might expect the anti-apoE antibody to cause an *increase* in the level of plasma active apoE. It is clear that Applicant contemplates the use of antisense nucleic acids as an agent capable of reducing the level of expression of apoE in an animal or patient. In the rebuttal, Applicant states "the nucleotide sequence of apoE is known so one of skill in the art would also fully expect to be able to use antisense technology to reduce apoE expression" (page 5, paragraph 3). However, it is noted that Applicant does not specifically refute the teachings of James, et al and Roush, et al (both references were cited in the previous Office Action). James, et al and Roush, et al teach that contrary to Applicants' assertion, the success of using antisense technology is very limited, even given the necessary sequence of the gene to be targeted. Furthermore, with regard to the use of an apoE-neutralizing antibody and in particular to claims 2 and 9, it is noted that Huang, et al (cited in the previous Office Action) teach that "optimal expression of apoE is crucial for maintaining normal metabolism of triglyceride-rich lipoproteins. Too little apoE impairs the clearance of triglyceride-rich lipoproteins and their remnants from plasma" (page 26393, column 1). Thus, in the absence of working exemplification, one skilled in the art cannot immediately accept the assertion that an apo-E neutralizing antibody can be used

efficaciously to treat an animal or a patient, because there is no way of predicting whether the patient will benefit from the treatment. There is a possibility, as Huang, et al teach, that administering such an agent to an animal or patient may upset normal metabolism in the animal or patient. Accordingly, one skilled in the art cannot practice the invention with a reasonable expectation of success without first performing extensive and undue experimentation.

There is no factual evidence that a reduction in the level of plasma active apoE can effectively reduce the production of VLDL in an animal or patient. The disclosures in the specification are based upon the results of studies published by Huang, et al. Huang, et al teach that the over-expression and accumulation of apoE3 causes a condition in mice that resembles hypertryglyceridemia (abstract). However, Huang, et al do not demonstrate that a reduction in the level of active apoE in the plasma of mice can cause a reduction in the level of VLDL in the plasma and as stated in the previous Office Action, neither does the specification. Furthermore, it is noted that Huang, et al do not conclude with certainty that the expression and accumulation of apoE causes hypertriglyceridemia in *humans*. It is well known in the art that the results of animal studies are often not correlative or even predictive of the results of clinical trials. Therefore, it can not be ascertained from the teachings of the specification that the invention can be used successfully to lower the level of apoE and thereby lower the level of VLDL in the plasma of a human. Also, neither the specification nor Huang, et al provide factual evidence that the expression and accumulation of apoE in mice or humans is causative of hyperlipidemia, *per se*. Accordingly, in the absence of exemplification, the disclosure is viewed as insufficient to enable the skilled artisan to use the invention commensurate in scope with the claims with a reasonable expectation of success.

Also, it is noted that Applicants state that "what was not known until the Applicants' discovery was that overexpression and accumulation of apoE actually *causes* hypertriglyceridemia by stimulating VLDL production and by impairing VLDL lypolysis" (paragraph bridging pages 7 and 8). The amended claims, on the other hand, are drawn to a method for reducing VLDL in an animal by administering an effective

amount of an undisclosed agent that causes the amount of plasma active apoE to decrease by an amount sufficient to reduce VLDL production. Therefore, it is noted that the claims do not require the undisclosed agent to stimulate VLDL lypolysis, but to merely impair the production of VLDL. It is not evident from the teachings of the specification that an agent that impairs production of apoE but does not stimulate VLDL lypolysis can be effective. Furthermore, it is noted that the specification does not teach by what amount apoE must be decreased to reduce the production of VLDL, which would severely limit one's success in screening putative agents since the specification provides insufficient guidelines for use in identifying a suitable agent.

In summary, there is no factual evidence of record indicating or providing a reasonable expectation that an undisclosed agent can be used to *effectively* reduce the level of active apoE in the plasma of an animal or patient. There is no factual evidence of record indicating or providing a reasonable expectation that the undisclosed agent can be used to reduce the level of active apoE in the plasma of an animal or patient to *effectively* reduce the production of VLDL in the animal or patient. There is no is no factual evidence of record indicating or providing a reasonable expectation that the undisclosed agent can be used to reduce the level of active apoE in the plasma of an animal or patient to reduce the production of VLDL in the animal or patient to *effectively* reduce the level of VLDL in the plasma of the animal or patient. In other words, there is not factual evidence that the undisclosed agent can be used *efficaciously* to treat an animal or patient suffering from a disease in which elevated levels of VLDL occur in the plasma of the animal or patient. Because of the unpredictability in the art of drug discovery, as evidenced by the teachings of Gura, et al, one skilled in the art cannot predict whether an animal or patient will benefit from a treatment according to the method claimed in the application. With regard to claims 7 and 8, there is no factual evidence of record indicating or providing a reasonable expectation that the undisclosed agent can be used to efficaciously to treat an animal or patient suffering from type IV hyperlipidemia or type IIb hyperlipidemia, respectively. With regard to the limitations in claims 4 and 11, there is no is no factual evidence of record indicating or providing a reasonable expectation that the undisclosed agent which reduces the level of active

apoE3, *per se,* in the plasma of an animal or patient can be used to *effectively* reduce the production of VLDL in the animal or patient or to efficaciously treat an animal or patient suffering from a disease. Because the art of drug discovery is highly unpredictable, one skilled in the art would not accept the assertion that an undisclosed agent can be used successfully to treat an animal or a patient suffering from a disease associated with the accumulation of plasma VLDL. Therefore, in the absence of exemplification that would suggest otherwise, there is no factual evidence that one skilled in the art can practice the claimed invention with a reasonable expectation of success without undue experimentation.

While the merit of the Amendment has received full consideration, Applicants' arguments are not persuasive, because the preponderance of evidence suggests that the subject matter of the claims is not adequately described so as to enable one skilled in the art to use the invention. Therefore, the disclosure fails to meet the enablement requirement of 35 USC § 112, first paragraph. For the reason set forth above, the rejection made in the previous Office Action paragraph in section 7 under 35 USC § 112, first is maintained.

Claim Rejections – 35 USC § 112, second paragraph

21. The Amendment filed under 37 CFR § 1.111 filed on May 7, 2001 in Paper No. 10 has received the Examiner's full and careful consideration, but the amendment to claims 1 and 5 is insufficient to overcome the rejection and Applicants' arguments are not found persuasive. The reason that the amendment to claims 1 and 5 is insufficient to overcome the rejection and that the arguments are not found persuasive is set forth below:

Applicants contend claims 1 and 5 have been amended to more particularly point out and distinctly claim the invention (page 3, paragraph 3). However, the amended claims are still indefinite because the claims still do not recite a positive process step that clearly relates back to the preamble of the claims. Claim 1, as amended now recites the limitation "an amount sufficient to reduce VLDL production in said host to reduce the plasma level of VLDL in said host". Claim 5, as amended now recites the

limitation "an amount sufficient to reduce VLDL production to treat said disease condition". The amendment of claims 1 and 5 to recite these limitations does not obviate the rejection, because the recitation of the limitations is not viewed as a recitation of a positive process step. As stated in the previous Office Action, amending claims 1 and 5, respectively, to recite, for example, the phrases "whereby the plasma level of VLDL in said host is reduced" and "whereby said host is treated" can obviate this rejection.

For the reason set forth above, the rejection made in the previous Office Action in section 9 under 35 USC § 112, second paragraph is maintained.

Claim Rejections – 35 USC § 102

21. The Amendment filed under 37 CFR § 1.111 filed on May 7, 2001 in Paper No. 10 has received the Examiner's full and careful consideration, but the amendment to claims 1 and 5 is insufficient to overcome the rejection and Applicants' arguments are not found persuasive. The reason that the amendment to claims 1 and 5 is insufficient to overcome the rejection and that the arguments are not found persuasive is set forth below:

Applicant argue that "nothing in the cited references teach that apoE is a target" (page 8, paragraph 4). Applicant also argues, "in relying upon a theory of inherency, the Office Action must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art" (page 9, paragraph 1).

Applicants contend claims 1 and 5 have been amended to more particularly point out and distinctly claim the invention (page 3, paragraph 3). However, the claims are still anticipated by Ditschuneit, et al, as evidenced by Pedreno, et al and Durrington, et al. The claims are still anticipated by Yoshino, et al and the claims are still anticipated by Connor, et al. In the rebuttal, Applicant states that "as amended, the claims are directed to a method for reducing the plasma level of VLDL in a host, and a method of treating a host suffering from a disease condition associated with elevated plasma level of VLDL, by administering to the host an effective amount of an agent which at least

reduces the amount of plasma active apoE in the host by an amount sufficient to reduce VLDL production" (page 7, paragraph 2). As set forth in the previous Office Action, Ditschuneit, et al, Yoshino, et al, and Connor, et al teach a method for reducing the level of VLDL in the plasma of an animal or patient by administering an effective amount of an agent to the animal or patient to reduce the level of active apoE in the plasma of the animal or patient.

Applicant states that "the claimed invention and the mechanism of gemfibrozil are not the same" (page 9, paragraph 3); however, the factual nature of this statement clearly cannot be determined, because the mechanism of the undisclosed agent, which is to be used in practicing the invention, is not known. As Applicant stated in the rebuttal, "a reference may anticipate a claim even if a feature recited in the claim is not specifically disclosed in the reference" (page 9, paragraph 1). It is noted, however, that the claims do not recite a limitation that requires the mechanism of action of the agent to be known and understood or to be different from the mechanism by which gemfibrozil acts. In fact, considering that the claims are drawn to an undisclosed and uncharacterized agent, it would not be possible to include such a limitation in the claims. Gemfibrozil, by whatever mechanism, reduces the level of apoE, and in reducing the level of apoE, the agent reduces the level of production of VLDL. Agreeably, Applicants state, in defining the basis for the concept of the invention, that "it necessary follows that reducing the plasma level of active apoE will also reduce the plasma level of VLDL" (page 4, paragraph 2). Nevertheless, Applicants question whether the gap in the teachings of the references is "filled with recourse to extrinsic evidence in order for the reference to serve as an anticipatory reference by inherency" (page 9, paragraph 1). The basis in fact and/or technical reasoning that reasonably supports the determination that the allegedly inherent characteristic of the prior art agents necessarily flows from the teachings of the applied prior art is that the prior art recognizes that while the mechanism(s) of action of the agent (e.g., gemfibrozil, pravastatin, dietary n-3 fatty acid) is/are either not known or not well understood, the agents can be used effectively to reduce both the level of plasma active apoE and the level of plasma VLDL in an animal or patient.

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

25. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (703) 305-3008. The examiner can normally be reached on Monday-Thursday, alternate Fridays, 8:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C. Caputa, Ph.D. can be reached on (703) 308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

DONNA WORTMAN
PRIMARY EXAMINER

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July 27, 2001

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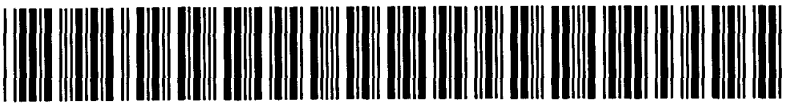

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